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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 09/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,422	CAWTHORNE ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005 and 20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,14-25,27-34 and 38-53* is/are pending in the application.

4a) Of the above claim(s) *34 and 38-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14-25,27-33,52* is/are rejected.

7)☒ Claim(s) *2,3,10,29 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/27/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.80

DETAILED OFFICE ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-33, 52, and 53) and election of the protein LOTM21 (as set forth in claim 29) in the replies filed on 07 April 2005 and 21 July 2005 is acknowledged. The traversal is on the ground(s) that any protein which exhibits the foregoing characteristics is encompassed by the claim, thus, the election of a single protein from claim 29 is onerous and unwarranted. Applicants further assert that it appears as though the Examiner is treating claim 29 as a composition of matter claim, whereas the claim merely recites different proteins identified in the presently disclosed methods.

This is not found persuasive. The restriction requirement, as presented on page 5, second full paragraph of the previous Office action mailed 26 January 2005, the protein sequences and combinations thereof as set forth in claim 29 are patentably distinct and unrelated. As such, alternative embodiments of the method of claim 1 wherein the differentially expressed protein or proteins are defined as one or a combination of the specific sequences set forth in claim 29 are patently distinct each from the other and therefore present an undue burden of search if searched together. The assertion that claim 29 has been treated as a composition of matter is not germane to the restriction requirement as claim 29 is identified as belonging to the invention of Group I, characterized as being drawn to a method of screening for an agent to determine its usefulness in treating insulin resistance.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example page 83, line 32 and page 84, lines 16 and 33. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 2 objected to because of the following informalities: Claim 2 recites "the agent is selected it if changes" in line 1 of the instant claims and should be replaced with --the agent is selected if it changes--. Claim 3 in also included under this objection due to its dependence from claim 2. Appropriate correction is required.

Claim 29 is objected to as the instant claim reads on non-elected protein and combinations of proteins rather the elected protein of LOMT21. For the purpose of continuing examination, claim 29 has been examined only to the extent of the elected protein, LOMT21.

Claim 53 is objected to as it does not conform to 37 C.F.R. §1.75 (c), as the instant claim depends from a canceled claim. Appropriate correction is required. The instant claim recites the limitation "the comparatively insulin sensitive subjects" in lines 1 and 2 of the claim, for which no other claim can provide an antecedent basis. As such, the instant claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-7, 14-25, 27-32, and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a biological sample comprising cellular tissue, does not reasonably provide enablement for a subcellular fraction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

Step b) of claim 1 recites "providing a biological sample comprising cellular tissue or a subcellular fraction thereof susceptible to insulin reaction. Further, Step c) of claim 1 recites "contacting the sample of step b) with an agent and identifying proteins which are differentially expressed in response to said agent". The scope of the instant claim includes the embodiment wherein a sample is comprised only of subcellular fractions

and rather than whole cells. In this particular embodiment, contacting a sample comprising only subcellular fractions with an agent as instantly would not result in an altered differential expression of proteins as the fractionated cells would no longer be capable of expressing protein. The instant specification provides examples only involve the treatment of lean and obese mice with the agent rosiglitazone by oral gavage for 7 days. All tissue, cell, and subcellular samples were prepared following the administration of the agent to live mice. See the instant specification, page 73, lines 14-27. As such no, working examples or protocols have been provided by the instant specification that would enable one of skill in the art to perform the above embodiment of the instantly claimed method. For one of skill in the art to perform the disclosed method as instantly claimed, a procedure would be required that allows for fractionated samples, further treated with a compound, to express proteins without any inhibition due to being in a fractionated state. Dreger sets forth a review of proteome analysis at the level of subcellular structures. In the review, the analysis of differential protein expression at subcellular fraction was limited to differential expression patterns that were already established prior to the time a cell sample was fraction. See Greger, page 589, column 1, line 1 through column 2, line 10. No procedure has found in the related arts that allows for the determination of differential expression patterns induced by an agent following the treatment of a fractionated sample by said agent.

In considering the factors for the instant claims:

(1) the quantity of experimentation necessary: In order to use the below described embodiment of the claimed invention one of skill in the art would require a procedure

that allows for fractionated samples, further treated with a compound, to express proteins without any inhibition or hindrance due to being in a fractionated state. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

(2) the amount or direction presented: The disclosure only provides direction for the treatment of tissue samples and live animals with compounds or agents that may alter expression patterns as a results of said treatment. No specific protocols are provided by the disclosure to establish differential protein expression patterns from a subcellular fraction treated with an agent after the subcellular fraction was prepared.

(3) the presence or absence of working examples: The disclosure provides working examples of the disclosed method wherein animals are exposed to an agent effecting the expression of proteins. No working examples are provided for the embodiment of the invention wherein a fractionated sample is exposed to an agent in order to establish a differential expression pattern.

(4) the nature of the invention: The nature of the invention is identifying differentially expressed proteins in response to an agent and is complex.

(5) the state of the prior art: The Prior art does not show any methods or protocols to establish differential protein expression patterns from a subcellular fraction treated with an agent after the subcellular fraction was prepared. For example, Dreger sets forth a review of proteome analysis at the level of subcellular structures. In the review, the analysis of differential protein expression at subcellular fraction was limited to

differential expression patterns that were already established prior to the time a cell sample was fraction. See Greger, page 589, column 1, line 1 through column 2, line 10.

(6) the relative skill of those in the art: The skill in the art of identifying differentially expressed proteins in response to an agent is high.

(7) the predictability or unpredictability of the art: The response of differentially expressed proteins to treatment with agents is highly unpredictable.

(8) the breadth of the claims: The scope of the claims include samples comprising cellular tissue and subcellular fractions thereof.

Therefore, the skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the disclosure lacks any description of a procedure for the determination of differential expression patterns induced by an agent following the treatment of a fractionated sample by said agent.

As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not provide any procedure for the determination of differential expression patterns induced by an agent following the treatment of a fractionated sample by said agent. Finally, said practitioner would turn to trial and error experimentation to determine such a procedure. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the limitation "the normal control animals are insulin sensitive littermates of the genetically mutated animals" in lines 1 and 2 of the instant claim. Claim 14, from which claim 15 depends, recites the limitation "the insulin resistant subjects... are animals which are insulin-resistant as a result of genetic mutation" in lines 1-3 of the instant claim. Since the term "genetically mutated animals" in claim 15 has antecedent basis provided by the above cited limitation from claim 14, the normal control animals, as recited in claim 15, are therefore insulin resistant genetically mutated animals. It is unclear from either claim how insulin sensitive normal control animals can also be litter mates of insulin resistant genetically mutated animals, as the two groups of animals (one mutated and one normal) are mutually exclusive of one another.

For the purpose of continuing examination, the Examiner has construed claim 15 to read as the normal control animals are insulin sensitive littermates.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 14, 16-20, 22, 33, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al.

The instant claims are drawn to methods of screening for an agent to determine its usefulness in treating insulin resistance comprising the steps of (a) identifying proteins which are differentially expressed in biological samples obtained from insulin resistant, normal or insulin sensitive subjects in response to a known treatment or compound which alters insulin sensitivity, (b) providing a biological sample comprising cellular tissue or a subcellular fraction thereof susceptible to insulin action, (c) contacting said sample with said agent and identifying proteins which are differentially expressed in response to said agent, and (d) comparing the results of steps (a) and (c) thereby identifying those agents which alter expression levels of said proteins towards that observed in an insulin resistant or insulin sensitive subject.

[Claims 1 and 17-20]: Wang et al. sets forth a study in Zucker rats and *ob/ob* and *db/db* nice focused on the possible role of neurones in the hypothalamic arcuate nucleus (ARC) which expresses neuropeptide Y (NPY). See Wang et al., page 10405, column 1, line 26 through column 2, 22. The thiazolidinedione BRL 49653 (rosiglitazone) induced hyperphagia and weight gain in obese, insulin-resistant Zucker rats but not in lean insulin-sensitive Zucker rats, wherein the response was related to altered expression levels of NPY, leptin and insulin. See Wang et al., Abstract. The samples used in experimental assays were blood and brain tissue isolated from the

above described animals. See Wang et al., page 1406, column 1, lines 14 through column 2, line 22. Plasma leptin, insulin, corticosterone, and NPY levels were measured from samples obtained from treated and control animals. See Wang et al., page 1406, column 1, lines 34, 35, 46, and 47, page 1406, column 2, lines 4-21, and page 1406 column 2 line 46 through page 1407, column 1, line 32. The discussion provided by Wang et al. compared the results of the measured expression levels of identified proteins to the response generated by the treatment of the above described rats with rosiglitazone. See Wang et al., page 1407, column 1, line 33 through page 1408, column 2, line 17 and Figures 1-3.

[Claims 2 and 3]: Wang et al. further disclosed that treatment with rosiglitazone may alter the expression levels of leptin, insulin, and corticosterone, wherein the observed 30%-40% falls in plasma insulin levels during treatment with rosiglitazone could contribute to hyperphagic and weight gain. Treatment of rats with rosiglitazone was hypothesized as contributing to the observed hyperphagia (broadly construed as insulin-sensitivity). See Wang et al., page 1407, column 2, line 22 through page 1408, column 1, line 13.

[Claims 4 and 5]: The study disclosed by Wang et al. included normal rats, insulin-resistant rats, and insulin sensitive rats obtained from Harlan Olac Ltd, Bicester, Oxon, U.K. See Wang et al., Abstract, page 1406, column 1, lines 15-22, and page 1406, column 2, line 47 through page 1407, column 1, line 34.

[Claim 14]: Wang et al. discloses that rats used in the study included mutants. See Wang et al., page 1405, column 2, lines 10-15.

[Claims 16, 17, and 22]: The experimental protocols disclosed by Wang et al. provided for the treatment of fatty and lean Wistar and Zucker rats with rosiglitazone by oral means. Additional control animals were given an equivalent volume of 10% sucrose. See Wang et al., page 1406, column 1, lines 14-57.

[Claim 33]: Wang et al. disclose preparing rosiglitazone with a 10% solution of sucrose for oral administration to rats. See Wang et al. page 1406, column 1, lines 25-30.

Claims 1, 6, 7, 18, 22, 23, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Stephens et al.

The instant claims are drawn to methods of screening for an agent to determine its usefulness in treating insulin resistance comprising the steps of (a) identifying proteins which are differentially expressed in biological samples obtained from insulin resistant, normal or insulin sensitive subjects in response to a known treatment or compound which alters insulin sensitivity, (b) providing a biological sample comprising cellular tissue or a subcellular fraction thereof susceptible to insulin action, (c) contacting said sample with said agent and identifying proteins which are differentially expressed in response to said agent, and (d) comparing the results of steps (a) and (c) thereby identifying those agents which alter expression levels of said proteins towards that observed in an insulin resistant or insulin sensitive subject. Further, the instant claims are drawn to abnormally sensitive subjects acquiring said sensitivity by exercise,

said subjects suffering from insulin-dependent type diabetes, and the relevant tissue is liver, skeletal muscle, or white or brown adipose tissue.

[Claims 1, 18, and 52]: Stephens et al. set forth a review focusing on a family of proteins of mammalian facilitative glucose transporters (GLUTs) whose expression is identified with the major insulin target tissues of fat and cardiac and skeletal muscle where is serves as the major mediator of glucose uptake. See Stephens et al., page 529, column 1, line 1 through page 530, column 1, line 19. Stephens et al. further set forth the role of GLUT expression and trafficking in relation to the insulin action within murines. See Stephens et al., Figure 2 and page 530, column 2, line 1 through page 532, column 1, line 3. A nonhydrolyzable glucose analog, [γS]GTP, is described as a compound used to stimulate activation of glucose transport in a manner similar to the effect of insulin. See Stephens et al., page 532, column 2, lines 14-56 and column and page 533, column 2, line 45 through page 534, column 1, line 12. Further, Stephens et al. described the discovery of novel proteins whose expression is restricted to GLUT4 vesicles, which is characterized in relation to insulin-sensitive and insulin-responsive glucose uptake, from fat and muscle cells. See Stephens et al., Table 2 and page 534, column 1, lines 13-45.

[Claims 6 and 22]: Stephens et al. provides for a discussion of GLUT 4 expression and transport in the context of normal and obese rats in relation to contractile activity (exercise), glucose uptake and insulin-response. See Stephens et al., page 539, column 1, lines 4-46.

[Claim 7]: Table 1 of Stephens et al. provides for the expression of GLUT 4 and identified specific activity within brown and white fat, skeletal muscle and liver tissues.

[Claim 23]: Stephens et al. also sets forth the role of GLUT4 expression and regulation in relation to non-insulin dependent diabetes. See Stephens et al., page 538, column 2, line 20 through page 539, column 1, line 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 14, 16-20, 22, 23, 27-33, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Wang et al or Stephens et al. in view of Linskens et al (U.S. Patent No. 5,744,300).

The instant claims are drawn to methods of screening for an agent to determine its usefulness in treating insulin resistance comprising the steps of (a) identifying proteins which are differentially expressed in biological samples obtained from insulin resistant, normal or insulin sensitive subjects in response to a known treatment or compound which alters insulin sensitivity, (b) providing a biological sample comprising cellular tissue or a subcellular fraction thereof susceptible to insulin action, (c) contacting said sample with said agent and identifying proteins which are differentially expressed in response to said agent, and (d) comparing the results of steps (a) and (c)

thereby identifying those agents which alter expression levels of said proteins towards that observed in an insulin resistant or insulin sensitive subject. Further, the instant claims are drawn to additional steps of isolating, and characterizing the differentially expressed proteins.

[Claim 27-32]: As discussed above, both Wang et al. and Stephens et al. set forth the identification of proteins differentially expressed in biological systems of insulin resistant, normal, or insulin sensitive subjects in response to a known treatment or compound that alters insulin sensitivity, contacting a sample from the biological systems to an agent, and further identifying those agents which alter the expression levels of said proteins towards that of insulin resistant or insulin sensitive subjects. However, neither Wang et al. nor Stephens et al. fairly teach additional steps of isolating, and characterizing the differentially expressed proteins.

Linskens et al. sets forth, in the context of senescence-related genes, methods of high-throughput screening to identify compounds which alter expression levels. See Linskens et al., Abstract and claim 1. Linskens et al. further provide for the isolation and characterization of the differentially expressed genes and related gene products. See Linskens et al., column 4, line 34 through column 5, line 11. Linskens et al. further sets forth the use of identified genetags correlated with known sequences for use in high-throughput assays to quantify differential gene expression in response to treatment with active compounds. See Linskens et al., column 13, line 44 through column 14, line 35. Identified genetag have been established for, amongst many others, human aldehyde

dehydrogenase 1 and human insulin-like growth factor binding protein 5. See Linskens et al., column 13, lines 13-43.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the methodology taught by Linskens et al. of isolating and characterizing differentially expressed identified by the methods taught by either Wang et al. and Stephens et al. because the isolating, characterizing, and high-throughput techniques taught by Linskens et al. are generally applicable to finding therapeutic agents related to insulin- and glucose-related conditions (such as diabetes), as taught by either Wang et al. and Stephens et al.

Conclusion

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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